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Genetics of Cerebral Cavernous Malformations: Current Status and Future Prospects

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Abstract

Cerebral cavernous malformations (CCM) are vascular lesions which affect up to 0.5% of the general population, predisposing to headaches, seizures, cerebral hemorrhages and focal neurological deficits. CCM occurs in both sporadic and familial forms; familial cases follow an autosomal-dominant mode of inheritance and are caused by mutations in *CCM1 (KRIT1)*, *CCM2 (MGC4607)*, or *CCM3 (PDCD10)*. Somatic mutations within the three *CCM* genes have been identified in CCM lesions from both sporadic and familial patients. We reviewed articles published in PubMed in English prior to March 2015 and provide an update on *CCM* mutations and the screening strategies used to identify them. Further, we summarize the specific clinical features related to *CCM* genotypes. As 5 to 15% of familial CCM cases remain genetically unexplained, we also discuss future approaches to expand understanding of the genetic architecture of CCM. Finally, we discuss possible genetic modifiers of CCM disease severity and progression. Understanding the genetic architecture of CCM is essential for an earlier diagnosis of the disease, predictive testing of at-risk patients, and design of targeted medical therapies of which there are currently none available.

Keywords

Cerebrovascular disease; Cerebral Cavernous Malformation; CCM

INTRODUCTION

Cerebral cavernous malformations (CCM) are enlarged vascular lesions consisting of closely clustered, abnormally dilated and leaky capillary caverns that affect up to 0.5% of the general population.[1] CCM can manifest as a broad range of symptoms typically in the

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2nd to 5th decade of life, including cerebral hemorrhage, seizures, chronic headaches and neurological deficits, among others.[2] However, around 50 – 80% of CCM cases are asymptomatic, and CCM lesions are often discovered incidentally on magnetic resonance imaging (MRI).[3] Symptomatic, hemorrhagic lesions are generally treated surgically, although lesions located in the brainstem are particularly challenging and associated with high surgical morbidity.[4] Currently, there is no approved medical therapy available for treating CCM.

Both sporadic and familial forms of CCM exist. Sporadic cases of CCM are characterized by a lack of family history of the disease and usually the presence of a single lesion on MRI,[5,6] although multiple lesions have been observed.[7,8] In contrast, familial cases mostly exhibit multiple lesions that show progression in both number and size over time.[9] Familial CCM follows an autosomal-dominant inheritance pattern with incomplete penetrance, and has been linked to heterozygous loss-of-function mutations in three different *CCM* genes: *CCM1/KRIT1*, *CCM2/MGC4607*, and *CCM3/PDCD10*.[10–13] However, 5–15% of familial cases cannot be explained by the three known CCM genes, suggesting the existence of additional CCM loci.[14]

CCM lesion genesis is thought to follow a "two-hit" mechanism, requiring biallelic germline and somatic mutations in one of the three known *CCM* genes.[15–17] Somatic mutations in CCM genes were identified in the endothelial cells of CCM lesion tissue, highlighting the importance of endothelial cells as the primary site of CCM lesion pathogenesis.[16–19]

A spectrum of mutation types have been identified within the three known *CCM* genes, allowing for better characterization of phenotype-genotype correlations. The wide variability in phenotypes seen among carriers of the same gene mutation also suggests the influence of additional genetic and/or environmental modifiers.[20–23] Patients with mutations in different *CCM* genes may follow a different clinical course, but genetic testing is often not undertaken for patients with multiple CCMs in clinical practice. In this review, we update and discuss the importance of screening the three *CCM* genes using different methods to identify mutations predisposing to CCM. We also highlight the main clinical symptoms according to *CCM* gene mutation status and additional clinical features associated with CCM. Finally, we discuss future prospects for elucidating the molecular basis of CCM as well as genetic modifiers of CCM disease severity and progression. Understanding the genetic architecture of CCM is essential for an earlier diagnosis of the disease, predictive testing of at-risk patients, and design of appropriate medical therapies of which there are currently none available.

From Discovery of CCM Loci to Recent Progress in Defining the Molecular Basis of CCM

Sporadic and familial CCM cases: genetic mutations in CCM-1, -2 or -3

Identification of CCM Loci—In 1995, the first CCM locus (CCM1) was identified on chromosome 7q by several groups studying large Hispanic and non-Hispanic families with multiple affected relatives.[24–26] Johnson and colleagues refined the 7q region of interest from approximately 40-cM to 4-cM, containing four potential candidate genes.[27] Shared

haplotypes were detected between affected members in three Hispanic CCM families, suggesting a common ancestral mutation.[27] Hispanic-American familial and sporadic CCM cases demonstrated inheritance of the same haplotype from a common ancestor by high-density microsatellite genotyping within 7q.[28] In non-Hispanic CCM families, some studies confirmed the linkage to 7q,[25,29,30] while others excluded this region, suggesting the presence of additional CCM loci.[31] In 1998, Craig and colleagues investigated linkage in twenty non-Hispanic Caucasian CCM families and reported two novel loci: CCM2 at 7p and CCM3 at 3q.[32] Additional studies replicated linkage to the CCM2 or CCM3 locus and also indicated genetic heterogeneity among non-Hispanic CCM families.[33,34]

Identification of CCM genes and mutations—In 1999, the *CCM1* gene or *KRIT1* (Krev Interaction Trapped 1) on chromosome 7q was discovered using a genomic sequence-based positional cloning strategy.[10] Seven different *CCM1/KRIT1* mutations were reported in 23 distinct CCM families, including the "common Hispanic mutation" (Q455X, rs267607203), which explains the majority of CCM cases occurring in Hispanic-American families of Mexican descent.[10] In 2001, computational and experimental analyses detected four additional coding exons in *CCM1/KRIT1*, resulting in corrected annotation of the *CCM1* genomic sequence, and the discovery of another novel frameshift mutation.[35]

In 2003, Liquori and colleagues selected eight candidate genes out of 55 identified at the 7p CCM2 locus, on the basis of biological relevance.[11] Sequence analysis identified eight different mutations in nine CCM families in the *CCM2/MGC4607* candidate gene, encoding malcavernin protein.[11] Denier and colleagues also identified *MGC4607* as the *CCM2* gene and reported 2 large deletions as well as eight point mutations in *CCM2* in 30 families with CCM.[12] In 2005, Bergametti and colleagues identified the *CCM3* gene or *PDCD10* (programmed cell death 10) on chromosome 3q, using high-density microsatellite genotyping in 20 CCM families.[13] A *de novo* deletion within *PDCD10* was identified as well as six deleterious mutations in non-Hispanic Caucasian CCM families.[13] Figure 1 shows the chronological milestones in the discovery of the molecular basis of CCM.

Overall, the majority of CCM patients have mutations in *CCM1*. Sequencing of coding exons and intron–exon junctions in genomic DNA of all three *CCM* genes has identified a mutation in 95% of familial cases and 57% of sporadic cases with multiple lesions.[2] In a screening study of 163 consecutive CCM patients, mutations were identified in 128 (78%), including 53% in *CCM1/KRIT1*, 15% in *CCM2/MGC4607,* and 10% in *CCM3/PDCD10*.[2] Among 122 CCM patients with identified mutations, 65% were in *CCM1*, 19% in *CCM2*, and 16% in *CCM3*.[14] Among sporadic CCM cases from two Italian studies, germline mutations were identified in 1.3% to 5.5% in *CCM1*, 2.5% to 2.6% in *CCM2*, and 0% in *CCM3*.[36,37] Studies in French, Swiss and German cohorts have reported similar findings.[2,7,14,38] Thus, a minority of sporadic cases is due to germline mutations in *CCM* genes, which could be inherited or de novo.

Not all disease-causing mutations are small coding changes detectable by sequencing. Other methods such as multiplex ligation-dependent probe amplification (MLPA), quantitative multiplex PCR of short fluorescent fragment (QMPSF) or array-based comparative genomic hybridization (array CGH) are required to detect larger insertions/deletions, duplications and

other copy number and structural changes associated with CCM.[39–43] MLPA studies in *CCM1-3* mutation-negative probands have detected large genomic deletions or duplications within all three *CCM* genes, indicating that large genomic rearrangements represent a major component of CCM disease.[40–42] For example, a common 78-kb deletion spanning exons 2–10 of *CCM2* has been found in 13% of CCM families screened in a US study,[40] while a larger screening study estimated that 18% of all mutations in *CCM1, CCM2,* or *CCM3* are due to large deletions.[14] Such large rearrangements can also encompass additional flanking genes,[44] which could contribute to the disease phenotype, such as in a rare syndromic case featuring both CCM and Greig cephalopolysyndactyly syndrome due to a large deletion on 7p14–13 encompassing both *CCM2* and *GLI3*.[43] In addition, cDNA sequencing may be necessary to characterize candidate intronic variants resulting in a splicing defect,[14] and can also reveal CCM mutations resulting from other types of genomic rearrangements.[3] For example, an intronic *CCM1* insertion causing extension of transcription into an intron and resulting in a premature stop codon was detected in a CCM family with multiple affected individuals who had CCM lesions on MRI but were asymptomatic.[3] Such findings expand the *CCM* mutation spectrum and highlight the importance of screening the three *CCM* genes using different methods to identify mutations.[3,14] The Angioma Alliance, a patient advocacy group for those affected with CCM, maintains a database of reported CCM mutations (www.angioma.org/mutation).

CCM pathogenesis: a two-hit mechanism

Until the early 2000's, the pathogenic mechanisms underlying CCM lesion genesis remained unknown. The presence of multiple lesions in familial and single lesions in sporadic CCM cases inspired the hypothesis that somatic mutations may contribute to CCM lesion genesis according to a "two-hit" mechanism, resulting in biallelic inactivation of one of the *CCM* genes in lesion cells. In 2002, Kehrer-Sawatzki and colleagues investigated for the first time DNA isolated from CCM tissue and identified two *CCM1/KRIT1* somatic mutations in a CCM lesion from a sporadic case.[45] Following these findings, several studies attempted to validate this "two-hit" mechanism hypothesis with varying success, likely due to limited sensitivity of genetic screening methods used at the time.[15,46–48] In 2005, Gault and colleagues reported a familial CCM case with a germline *CCM1*-CHM mutation that also harbored a somatic *CCM1* deletion in surgically-resected CCM lesional tissue.[15] These findings strongly supported the "two-hit" hypothesis in CCM lesion genesis and were replicated in other studies, showing biallelic germline and somatic mutations in *CCM1*, and also in *CCM2* or *CCM3* in familial cases.[16,18] Akers and colleagues also found that these somatic mutations occurred in endothelial cells from CCM tissue by laser capture microdissection, highlighting endothelial cells as the primary site of CCM lesion pathogenesis.[16,18] Even with highly sensitive next generation sequencing technology, somatic mutations were detected only in a fraction of endothelial cell DNA from CCM tissue, pointing out the heterogenous nature of the lesion. Recently, McDonald and colleagues confirmed that sporadic cases of CCM can also follow this "two-hit" mechanism, reporting the presence of one or two biallelic somatic mutations in CCM lesions from sporadic cases.[17]

Mouse models of CCM also support the "two-hit" hypothesis, as heterozygous *Ccm1* or *Ccm2* mutant mice do not spontaneously develop CCM lesions.[47,49] Indeed, *Ccm1* heterozygous mice need to be crossed into a mismatch repair-deficient *Msh2*^{−/−} or *Trp53*^{−/−} background, increasing the rate of somatic mutations, to exhibit CCM lesions.[47,49] However, *Ccm2*^{+/−} */Msh2*^{−/−} mice did not manifest CCM lesions in contrast to *Ccm2*^{+/−} */Trp53*^{−/−}mice, showing the complexity of modelling human inherited diseases such as CCM in mouse models.[49,50] Recently, Shenkar and colleagues reported that *Ccm3* heterozygous mice exhibit CCM lesions without *Trp53*^{−/−} or *Msh2*^{−/−} background,[51] suggesting other pathogenetic mechanisms underlying CCM lesion genesis and echoing phenotypic differences in severity between CCM1/2 and CCM3 disease discussed below.

Genotype-phenotype correlations: wide variability among CCM patients

Sporadic vs. familial CCM cases—Sporadic cases of CCM are characterized by a lack of family history of the disease and usually the presence of a single lesion on MRI,[5,6] although multiple lesions have been observed.[7,8] In contrast, familial cases mostly exhibit multiple lesions that can appear de novo and increase in size over time.[9] Other imaging phenotypes have been reported to differ between sporadic and familial CCM cases. Petersen and colleagues reported a higher incidence of developmental venous anomaly associated with a CCM lesion in sporadic (44%) compared to familial *CCM1*-CHM cases (1.2%).[6] More recently, patients with familial *CCM1*-CHM were reported to have a higher prevalence of white matter abnormalities (15.4%) in comparison to age-matched cohorts of sporadic CCM (2.5%) and healthy controls (2.1%); adjustment for vascular risk factors did not explain the increased frequency of white matter abnormalities among familial cases.[52] The reasons explaining these differences between sporadic and familial CCM cases are unknown, however they suggest the possibility of a different developmental mechanism underlying CCM pathogenesis for sporadic and familial cases.

***CCM1* and *CCM2* mutation carriers—**Over the last decade, studies have started to describe phenotypic differences by *CCM* gene mutation status. Most of these studies initially focused on CCM cases due to mutations in *CCM1* and *CCM2*, as those genes were discovered first and are the most common causes of familial CCM.[2,53]

In 2004, Denier and colleagues evaluated for the first time genotype-phenotype correlations in a large Caucasian cohort of 202 familial CCM subjects harboring *CCM1/KRIT1* mutations.[53] Most *CCM1* mutation carriers were symptomatic (62.4%), presenting initially with seizures (in 55% of cases) and cerebral hemorrhages (32%), followed by focal neurologic deficits (9%) and headaches (4%); the mean age of clinical onset was 29.7 years.[53] The number of CCM lesions was highly variable: 84.6% of subjects had two or more lesions on MRI, 26 subjects (12.9%) harbored only one lesion, and five subjects (2.5%) had no lesions.[53] In 2006, the identification of the third *CCM* gene enabled evaluation of genotype-phenotype correlations between *CCM1*, *CCM2* and *CCM3* mutation carriers.[2] The number of symptomatic subjects was lower in the *CCM2* group (55.2%) in comparison to *CCM1* (63.4%) and *CCM3* (67.9%) groups; however, the initial clinical symptoms were similar among the three groups.[2] Further, *CCM2* mutation carriers had a lower number of gradient-echo sequence lesions in comparison to *CCM1* or *CCM3* mutation

carriers, and the number of lesions increased more quickly with age in *CCM1* than in *CCM2*.[2] These results suggested overall that *CCM2* mutation carriers may have a milder phenotype than *CCM1* and *CCM3* mutation carriers.

In addition to the main clinical symptoms related to the cerebral lesions, other clinical features can occur in CCM patients. In 1999, hyperkeratotic cutaneous capillary venous malformation (HCCVM), a distinctive cutaneous vascular malformation composed of abnormal capillaries and venous-like vessels, was described in 4 French CCM families.[54] Genetic linkage analysis mapped HCCVM to the CCM1 locus on chromosome 7q, suggesting that both HCCVM and CCM were due to the same genetic abnormality.[54,55] The mutation causing CCM+HCCVM was discovered in exon1 of *KRIT1* causing an early premature stop codon; downstream mutations in *KRIT1* only seemed to be linked to the CCM phenotype in these families, suggesting a possible molecular-phenotypic correlation.[55] Others have also reported cutaneous vascular malformations in *CCM1* mutation carriers, including café-au-lait skin lesions, capillary malformations, venous malformations, or cavernous hemangiomas.[56–61] Interestingly, HCCVM has only been reported in *CCM1* patients, suggesting that HCCVM may be a specific clinical feature of CCM1 disease.[59] Thus, in a subset of CCM1 families, there is an additional risk of approximately 40% for coexisting cutaneous vascular lesions,[55] some of which are cosmetic but others may cause functional problems. Retinal cavernomas have also been associated with CCM, and found in approximately 5% of familial CCM cases with mutations in any of the three *CCM* genes.[62] Familial CCM cases carrying a *CCM1* mutation can also present with multiple vertebral and/or spinal cavernous angiomas.[20,56,58,63–65] Spinal cavernous angioma has also been reported in a *CCM2* mutation carrier.[58] Further, hepatic angiomas have been observed in *CCM1* patients.[64,65] The presence of angiomas in the brain, spinal cord, skin, retina, vertebral column, and liver suggests CCM vascular involvement in numerous tissues both within and outside the central nervous system (CNS). The extra-CNS involvement may pose additional risks to CCM patients, and also serve as a marker for possible CNS involvement in otherwise asymptomatic cases.

Recent insights: CCM3, the most severe form of CCM disease—Until recently, little was known regarding the phenotypes of CCM associated with *CCM3* mutations, as the *CCM3/PDCD10* gene was the last gene to be discovered and the number of *CCM3* mutation carriers was limited.[2,66–72] Recent case series have described a number of clinical features specific to *CCM3* patients.[21,42,51,73] Riant and colleagues reported that around 90% of *CCM3* patients presented with multiple CCM lesions and, as previously suggested,[2] cerebral hemorrhage was the initial manifestation in patients under 20 years of age.[73] A second study also suggested that children with *CCM3* mutations had significantly more CCM lesions in comparison to children with *CCM1* mutations.[74] Other studies supported the early-onset of clinical features in *CCM3* patients,[42] and a higher risk of early-onset cerebral hemorrhage in comparison to *CCM1* and *CCM2* patients.[21,51] Shenkar and colleagues also reported that *CCM3* patients had a higher risk of recurrent bleeding after a first hemorrhage.[51] Additional clinical features related to *CCM3* were also described, including presence of skin lesions as previously described,[59] severe scoliosis that can lead to spinal fusion, cognitive disability, and presence of multiple meningiomas or other brain tumors.[21,51,73] While skin lesions have

also been reported in *CCM1* and *CCM2* patients, these other features appear specific to *CCM3* patients. Thus, CCM3, although more rare than CCM1 and CCM2, appears to be associated with more specific and severe phenotypes of CCM disease, as well as an earlier age of onset.

Future Prospects

Other CCM genes?

As discussed above, approximately 20% of familial or sporadic cases with multiple CCMs screened have no genetic mutation identified.[2] Some of the cases in which a mutation is not found are likely due to technological issues and mutation type, but others probably represent further genetic heterogeneity of the disease and suggest the possibility of other CCM loci. Ethnic differences have been reported in CCM genetics, supporting this hypothesis and providing an avenue toward identification of new CCM genes.[75] Recently, a study in Japanese CCM cases with multiple lesions found that *CCM2* mutations seem to be more prevalent than *CCM1* or *CCM3* mutations, compared to Caucasian CCM cases.[76] In this study, mutations in *CCM1*, *CCM2* and *CCM3* accounted for 12.5%, 37.5% and 12.5% of the sporadic multiple CCM cases, respectively, in comparison to 20%, 30% and 10% of the familial cases.[76] Thus, nearly 40% of Japanese CCM cases screened lacked a mutation within the three known *CCM* genes,[76] which is twice the frequency in Caucasian CCM patients.

Overall, the fact that: 1) a fraction of familial CCM remain genetically unexplained, and 2) the fraction explained by mutations in *CCM-1, -2 and -3* genes may differ by ethnicity, indicates that other *CCM* genes remain to be discovered. For example, Gianfrancesco and colleagues reported a case of a 30-year-old female patient that exhibited CCM lesions and premature ovarian failure with a balanced translocation involving chromosomes 3 and X.[77] Any causative mutation or genomic rearrangements in the *CCM1*, *CCM2* and *CCM3* genes were excluded for this patient, suggesting that a different gene was responsible for CCM.[77] Characterization of this translocation by fluorescence *in situ* hybridization revealed an interruption of *ZPLD1* (zona pellucida-like domain containing 1), and expression levels of *ZPLD1* were reduced 2.5-fold in lymphoblastoid cells from the CCM patient as compared to those in healthy controls.[77] However, no mutation was detected in *ZPLD1* when screening CCM-affected families negative for *CCM1*, *CCM2* and *CCM3* mutations, suggesting that CCM due to *ZPLD1* mutations might be relatively uncommon,[77] or that disruption of the function of a different gene than *ZPLD1* underlies the CCM phenotype in this patient. Further studies are needed to establish the function of the *ZPLD1* gene and confirm its possible role in CCM pathogenesis. With the recent advent of high-throughput exome and genome sequencing for the discovery of genes underlying rare Mendelian disorders, we anticipate that the discovery of novel CCM genes will provide future directions for CCM research.

Genetic modifiers in CCM disease severity and progression

There is a wide variability in phenotypes among CCM patients, even among those with the same *CCM* gene mutation.[20–23] The reasons for this variability are unknown, but likely

include other genetic, environmental or lifestyle factors. Balasubramanian and colleagues described two CCM families presenting with highly variable manifestations of a *CCM1/ KRIT1* mutation, ranging from tonic-clonic seizures at 18-months of age to asymptomatic.[20] We recently reported an association of cardiovascular risk factors, such as obesity and systolic blood pressure, with the number of CCM brain lesions in a cohort of 185 familial Hispanic patients, all harboring the *CCM1* common Hispanic mutation (CHM).[22] In our cohort of *CCM1*-CHM mutation carriers, 63.2% of subjects were symptomatic at presentation with intracerebral hemorrhage as the main clinical symptom leading to CCM diagnosis; lesion burden ranged from 0 to 713 on susceptibility-weighted MRI.[22] Interestingly, a rare case of CCM monozygotic twins harboring a *CCM1/KRIT1* mutation allowed comparison of disease manifestation and clinical course in the presence of an identical genetic background.[78] The initial manifestation was seizures at the age of 19 years for both twin sisters, and each had an identical number of two CCM brain lesions.[78] However, the localization of CCM lesions and clinical course were different, probably due to the random nature of somatic mutations.[78] In contrast to the wider intrafamilial variability usually observed between siblings, these findings show greater similarity of disease onset in monozygotic twins, suggesting the influence of additional genetic modifiers in non-twin siblings.[78] In *CCM3* disease, a three generation family segregating a *CCM3* mutation was reported, showing a wide spectrum of clinical manifestations, including acute childhood cerebral hemorrhage in the proband, skin lesions in the mother, and multiple meningiomas in the maternal grandfather.[21]

Additional genetic variation either within the *CCM1/2/3* genes or in CCM signaling pathway genes may explain phenotypic differences between *CCM1/2/3* mutation carriers.[23,79] A large Italian family, consisting of 15 CCM subjects harboring a *KRIT1/CCM1* deletion and 8 subjects without the causative mutation, was screened for additional genetic variation within *CCM1*, *CCM2* and *CCM3* genes.[79] Numerous genetic variations were identified in the three *CCM* genes, which may modify expression or function of the CCM1/CCM2/CCM3 protein complex, thus explaining the observed phenotypic variability.[79] However, additional studies in other large CCM families and functional studies are needed to draw stronger conclusions. Recently, we investigated common genetic variation in inflammation and immune response pathways in 188 Hispanic patients harboring the *CCM1*-CHM mutation,[23] as those pathways play an important role in CCM pathogenesis.[80–82] We identified common variants associated with markers of CCM disease severity, including history of intracerebral hemorrhage, total number of CCM lesions, and total number of large lesions (5mm in diameter). In particular, rs9823731, a common intronic polymorphism in the TGF-β receptor 2 gene (*TGFBR2*) was associated with all three markers of CCM1 disease severity examined,[23] supporting the involvement of TGF-β signaling in CCM disease, as previously suggested.[83] Thus, TGFBR2 might be a key participant in the mechanism underlying CCM disease severity and phenotype variability.

Many studies have investigated the function of CCM proteins, their binding partners and the potential mechanisms through which these proteins may act within blood vessels to lead to CCM lesion formation, as extensively reviewed elsewhere.[84,85] These recent advances in CCM protein signaling suggest new candidate modifiers of CCM disease to explore. As an

example, the Heart of Glass (HEG) receptor has been demonstrated to interact with CCM1, CCM2 and CCM3 proteins in a signaling pathway involved in heart and vascular development.[86,87] Zheng and colleagues investigated the role of HEG in CCM formation by using mouse models and human studies of patients with familial CCM.[87] The study revealed HEG as one of the upstream activators of CCM signaling but did not find a role for HEG in the postnatal pathway underlying CCM pathogenesis.[87] These findings suggest that other modulators of CCM signaling and CCM pathogenesis remain to be discovered.[87]

Conclusions

Over the last decade, significant progress has been made in defining the molecular basis of CCM and identifying disease mutations within the *CCM1/KRIT1*, *CCM2/MGC4607* and *CCM3/PDCD10* genes. Recent studies have indicated the importance of systematically including different mutation screening methods to increase the chance of identifying insertions, deletions and other large genomic rearrangements and provide a comprehensive CCM genetic diagnosis. It is now apparent that *CCM3* cases can present earlier and with a more severe phenotype than *CCM1* and *CCM2* cases, but more clinical studies in larger cohorts of well-phenotyped sporadic and familial CCM cases are needed to further investigate genotype-phenotype correlations. Moreover, it is of particular interest to examine other environmental and genetic modifiers in CCM disease severity and progression, which may explain the significant phenotypic heterogeneity of the disease and provide insight into the natural history and pathophysiology of CCM. Knowing the specific genetic mechanisms underlying different forms of CCM disease, gene targets, and whether phenotypes differ by gene mutation will be important for targeted design of specific medical therapies to help slow or prevent CCM lesion formation and progression.

Acknowledgments

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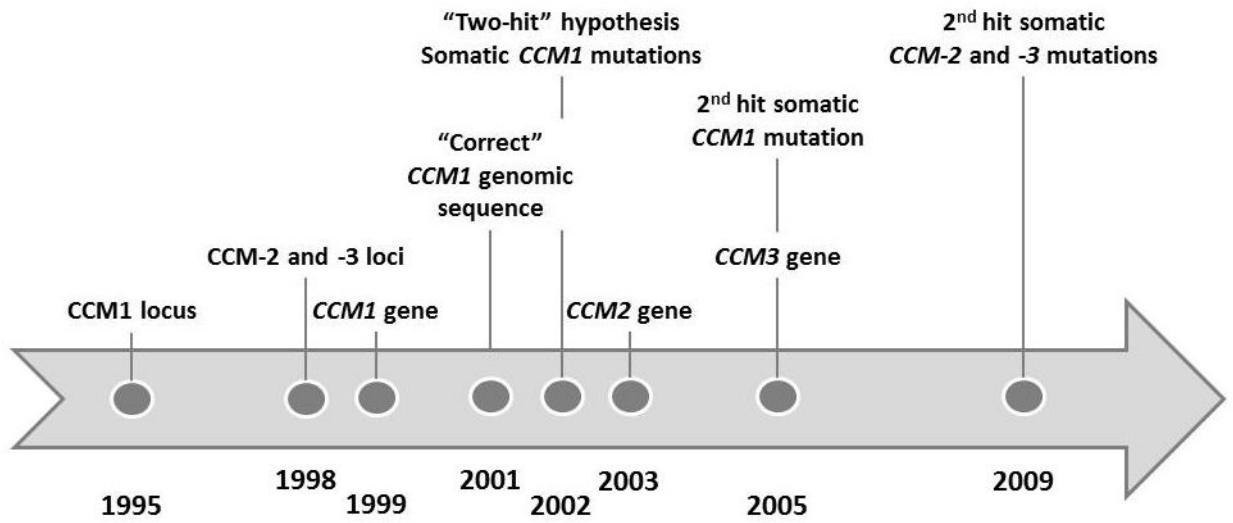
Figure 1.
Chronological discovery of CCM molecular basis